



Original Article

Phase I trial of concurrent stereotactic body radiotherapy and nelfinavir for locally advanced borderline or unresectable pancreatic adenocarcinoma



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ABSTRACT

Introduction: The HIV protease inhibitor nelfinavir (NFV) displays notable radiosensitizing effects. There have been no studies evaluating combined stereotactic body radiotherapy (SBRT) and NFV for borderline/unresectable pancreatic cancer. The primary objective of this phase I trial (NCT01068327) was to determine the maximum tolerated SBRT/NFV dose, and secondarily evaluate outcomes.

Methods: Following initial imaging, pathologic confirmation, and staging laparoscopy, subjects initially received three 3-week cycles of gemcitabine/leucovorin/fluorouracil; patients without radiologic progression received 5-fraction SBRT/NFV. Dose escalation was as follows: (1) 25 Gy/625 mg BID ×3wks; (2) 25 Gy/1250 mg BID ×3wks; (3) 30 Gy/1250 mg BID ×3wks; (4) 35 Gy/1250 mg BID ×3wks; (5) 35 Gy/1250 mg BID ×5wks; and (6) 40 Gy/1250 mg BID ×5wks. Pancreaticoduodenectomy was performed thereafter if resectable; if not, gemcitabine/leucovorin/fluorouracil was administered.

Results: Forty-six patients enrolled (10/2008–5/2013); 39 received protocol-directed therapy. Sixteen (41%) experienced any grade ≥2 event during and 1 month after SBRT. Four grade 3 and both grade 4 events occurred in a single patient at the initial dose level. 40 Gy/1250 mg BID ×5wks was the maximum tolerated dose. Five patients had late gastrointestinal bleeding ($n = 2$ superior mesenteric artery pseudoaneurysm, $n = 1$ disease progression, $n = 1$ lower GI tract, $n = 1$ unknown location). The median overall survival was 14.4 months. Six (15%) patients recurred locally; median local failure-free survival was not reached. The median distant failure-free survival was 11 months, and median all failure-free survival was 10 months.

Conclusions: Concurrent SBRT (40 Gy)/NFV (1250 mg BID) for locally advanced pancreatic cancer is feasible and safe, although careful attention to treatment planning parameters is recommended to reduce the incidence of late gastrointestinal bleeding.

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Neoadjuvant chemoradiation therapy is an attractive approach to manage locally advanced pancreatic cancer (LAPC) [1]. Not only can it allow patients with borderline resectable (BR) or unresectable (UR) disease to undergo resection, it may also reduce the rate of positive margins [2]. Selecting non-progressors in a more refined manner may better avoid surgical morbidities [3–5]. It is also more favorable in light of the notable disadvantages of adjuvant therapy, such as suboptimal receipt of chemoradiation

owing to surgical complications as well as the postoperative hypoxic environment [6].

Additionally, neoadjuvant treatment better favors the delivery of stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy, which is a highly conformal modality that affords low doses to surrounding organs-at-risk [7–8]. It has the major advantages of avoiding a protracted interval from diagnosis to surgery, along with increased patient convenience and enhanced cost-effectiveness [9].

Numerous prospective trials have reported the safety and efficacy of neoadjuvant SBRT for LAPC, particularly when delivered with 3–6 fractions [10]. However, tumor control and response rates remain relatively low. To improve upon these outcomes,

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dose-escalation is theoretically possible but often comes at the cost of greater toxicities; another approach is to administer radiosensitizer(s) in efforts to improve the therapeutic ratio. The human immunodeficiency virus (HIV) protease inhibitor NFV (NFV) interferes with PI3K-Akt signaling, which is normally involved in cellular growth and metabolism [11]. Multiple preclinical studies have demonstrated radiosensitizing effects, including in pancreatic cancer cells [12–14] and those that specifically received single-fraction ablative (8 Gy) radiotherapy (RT) [13]. Based on prospective trials in HIV patients, it is tolerated well [15]; moreover, many prospective investigations of other neoplasms have illustrated encouraging safety and efficacy of NFV with RT [16–21].

To date, there has been one phase I [22] and phase II [23] study evaluating NFV in LAPC, which displayed satisfactory results. However, both these studies utilized conventionally fractionated RT without ablative dosing. Because the fractional doses in SBRT are equivalent or higher than those achievable by conventional fractionation, there could be incremental improvements in durable tumor control or potentially even survival [24]; the addition of NFV in such settings may be even more pronounced. This is the first known study of combined NFV and SBRT for LAPC; the primary objective of this phase I trial was to assess the safety of this regimen and secondarily evaluate outcomes.

Materials & methods

Study participants

This was an Institutional Review Board approved phase I trial of concurrent NFV and SBRT for BR or UR LAPC (ClinicalTrials.gov number NCT01068327). Eligible patients were ≥ 19 years of age with newly diagnosed, pathologically confirmed BR or UR (as defined by the National Comprehensive Cancer Network [25]) non-metastatic pancreatic adenocarcinoma not exceeding 8 cm in maximal dimension. Additional criteria were the Karnofsky performance status of $\geq 60\%$ and serum laboratory values appropriate to receive chemotherapy. Patients with biliary or gastroduodenal obstruction were allowed if drainage or surgical bypass had been performed prior to starting SBRT. Patients with prior malignancy were also allowed, provided therapy was completed >5 years prior to enrollment and there was no clinical evidence of that malignancy. Exclusion criteria were patients who had received prior RT to the area (defined as disease overlap with the 20% isodose line), uncontrolled intercurrent illnesses (such as history of significant bowel pathology, including bleeding/ulcers), HIV infection, allergies to chemotherapy or antiemetics, inability to provide informed consent, or pregnant/nursing women. Additionally, patients receiving medications known to be contraindicated with NFV, along with those not able to undergo staging laparoscopy and fiducial marker implantation for any reason, were also considered ineligible.

Study procedures

All patients underwent initial workup by a medical, surgical, and radiation oncologist with a complete history and physical examination. Blood counts and chemistries along with CA 19-9 level were obtained, in addition to pathologic diagnosis and imaging (contrast-enhanced 3 phases, i.e. arterial, venous, and delayed phase computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (n = 20)). Patients then underwent staging laparoscopy to confirm lack of metastatic peritoneal disease, along with placement of two fiducial markers (Cook Medical, platinum embolization coil, 0.45 \times 5 mm) in the pancreas around the mass approximately two centimeters apart.

An proton pump inhibitor was started at the time of SBRT and continued for 1 month.

Patients initially received three cycles of 3-week chemotherapy with intravenous gemcitabine 750 mg/m² (females) or 900 mg/m² (males) over 30 minutes on days 1 and 8, calcium leucovorin 50 mg/m² over 30 minutes on days 1 and 8, and 5-fluorouracil 2700 mg/m² over 24 hours on days 1 and 8. Restaging CT and/or MRI were subsequently performed; patients were removed from the study in case of disease progression (defined per the Response Evaluation Criteria in Solid Tumors, or distant metastatic disease).

Provided there was no progressive disease, patients then started on oral NFV for two weeks prior to initiating SBRT. Pharmacokinetic studies confirmed appropriate concentrations of plasma NFV in each patient [26]. The dose escalation schema for this study was as follows: (1) 25 Gy + 625 mg BID NFV for 3 weeks; (2) 25 Gy + 1250 mg BID NFV for 3 weeks; (3) 30 Gy + 1250 mg BID NFV for 3 weeks; (4) 35 Gy + 1250 mg BID NFV for 3 weeks; (5) 35 Gy + 1250 mg BID NFV for 5 weeks; and (6) 40 Gy + 1250 mg BID NFV for 5 weeks. The standard 3 + 3 dose-escalation design was used; however, if the previous patient had not been clinically evaluated for at least one month, the next patient was enrolled on the same dose level. Twenty patients were enrolled at the highest dose level to most completely assess safety and efficacy, three of which were removed from protocol therapy following discovery of progressive/distant disease.

SBRT treatment planning consisted of a four-dimensional CT simulation (4DCT, 2–3 mm slice thickness) with custom immobilization devices (e.g. BodyFIX™, Elekta, Stockholm, Sweden) and intravenous/oral contrast. Target volume delineation was performed in accordance with the International Commission on Radiation Units and Measurements Report 50. Elective nodal irradiation was not performed [27]. The gross tumor volume (GTV_{primary} and GTV_{nodes} (≥ 1 cm)) was contoured using a combination of all available information on CT, MRI, and/or PET/CT imaging, along with clinical and endoscopic information when available. The integrated clinical tumor volume (CTV) was constructed from the aforementioned GTVs, additionally contouring the areas between them, along with additional margins obtained from 4DCT information to compensate for internal organ motion. The planning target volume (PTV) provided a 6 mm margin around the integrated CTV to compensate for variability in treatment setup, with exception at the gastric and duodenal interfaces (adjusted to avoid overlap with these areas). The prescribed doses ranged from 5 to 8 Gy \times 5 daily fractions (corresponding to biologically effective doses of 37.5 Gy, 48 Gy, 59.5 Gy, and 72 Gy); although the prescribed dose was to cover at least 95% of the PTV, 93% was acceptable for technically challenging circumstances related to bowel dose constraints. The recommended maximum and median doses were 110% and 100%, respectively. SBRT doses took into account tissue inhomogeneity corrections. Organs at risk were contoured in accordance with Radiation Therapy Oncology Group (RTOG) guidelines [28]. Dose constraints were from previous studies [27,29–32], SBRT dose tolerance publications [33], and RTOG 0631 [34]. Of note, no more than 5 cc of the stomach/small bowel was allowed to receive higher than 32 Gy. Owing to the balance between bowel dose and PTV coverage, however, additional duodenal dose constraints could be utilized (Supplementary Table 1). The percent of total kidney volume (sum of the left and right kidney volumes) receiving 15 Gy (3 Gy per fraction) was required to be less than 35% of the total kidney volume. The maximum dose to any point within the spinal cord was not allowed to exceed 15 Gy (3 Gy per fraction). At least 700 ml or 35% of the normal liver was required to receive a total dose less than 15 Gy (3 Gy per fraction). SBRT was delivered on a Novalis linear accelerator with a M3 multileaf collimator and daily image guidance using ExacTrac orthogonal kilovoltage imaging (BrainLAB, Heimstetten, Germany). Because the breathing

patterns were adequate in all patients, respiratory-gated delivery was used.

Follow-up

While on therapy, patients were seen weekly by a medical and radiation oncologist, with toxicity assessment per the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Patients underwent repeat CT and/or MRI imaging at 4 weeks following SBRT completion to evaluate for resectability at the surgical oncologist's discretion; if considered resectable, pancreaticoduodenectomy or partial pancreatectomy was performed 5–8 weeks following SBRT completion, followed by 3 more cycles of 3-week adjuvant gemcitabine/leucovorin/fluorouracil. If unresectable, gemcitabine/leucovorin/fluorouracil was delivered indefinitely pending tolerance and patient/physician preference. The chemotherapy regimen was selected from results of an institutional phase I protocol [35]. In either case, patients underwent surveillance contrast-enhanced CT and CA 19-9 every three months thereafter.

Pathologic response

For patients who underwent surgical resection, pathological response of the tumor to neoadjuvant therapy was re-evaluated by an experienced gastrointestinal pathologist. The pathological response score was assigned from 0 to 9, which was generated from the following three categories (tumor gland dropout, tumor shrinkage, and global tumor kill). Tumor gland dropout was scored as the following: (0) >90% of tumor nests back-to-back (minimal dropout, densely spaced), (1) 50–90% of tumor nests back-to-back (mild dropout), (2) 10–49% of tumor nests back-to-back (moderate dropout), and (3) <10% of tumor nests back-to-back (marked dropout, hypodense). Tumor shrinkage was quantified as follows: (0) >90% tumor cells with abundant cytoplasm, large multicellular glands (not shrunken), (1) 50–90% tumor cells with abundant cytoplasm, large multicellular glands (mildly shrunken), (2) 10–49% tumor cells with abundant cytoplasm, large multicellular glands (moderately shrunken) and (3) <10% tumor cells with abundant cytoplasm, large multicellular glands (markedly shrunken). Lastly, global tumor kill was defined as follows: (0) No definite response (poor to no response), (1) minimal response (some fibrosis, moderate amount of cancer present), (2) moderate response (minimal residual cancer present) and (3) complete response (no residual cancer identified).

Statistical analysis

The primary endpoint of this trial was to evaluate safety and toxicity profiles. A dose-limiting toxicity (DLT) was defined as (1) CTCAE grade ≥ 4 hematologic toxicity, (2) CTCAE grade ≥ 3 non-hematologic toxicity except grade ≥ 4 nausea/vomiting/diarrhea not controlled with medical treatment, or (3) a ≥ 1 week break from SBRT that was possibly, probably, or definitely related to SBRT/NFV. Occurrence of a DLT required entry of three additional patients to the particular dose level at which it occurred; if two instances in the same dose level were experienced, de-escalation to the prior dose level was obligated. The maximum tolerated dose (MTD) of NFV/SBRT was defined as the highest dose level at which no greater than one DLT was experienced. Secondary endpoints included analysis of local (in-field, including in-field primary and nodal disease, if applicable) failures by overlaying the area of suspected recurrence with the SBRT field; all other relapses were categorized as distant (out-of-field). Consequently, distant failure-free survival (DFFS), (overall) failure-free survival (FFS), and overall survival (OS) were computed actuarially by the Kaplan–Meier method

and compared with the log-rank test. Local failures were evaluated in cumulative incidence format using competing risk methodology. All statistics were performed with SAS version 9.4 (Cary, NC) and denoted $p < 0.05$ as statistically significant.

Results

Fig. 1 demonstrates a flow diagram of the trial. Altogether, 46 patients consented to enroll (all but one (involving the pancreatic body) had disease in the pancreatic head). Seven patients were taken off trial prior to undergoing SBRT/NFV, with the most common reason being disease progression (of these seven patients, one did not receive any therapy, three received 1 cycle and three completed 3 cycles of induction chemotherapy). Thus, 39 patients underwent SBRT/NFV per protocol and were subsequently analyzed (Table 1).

Toxicity assessment is detailed in Table 2. There were 21, 11, and 2 instances of grades 2, 3, and 4 toxicities, respectively. Of the 39 patients, 16 (41%) patients experienced any grade ≥ 2 adverse event. Of note, all grade ≥ 3 adverse events had started prior to receiving concurrent SBRT/NFV. Four instances of grade 3 events, plus both grade 4 events, occurred in a single patient at the initial dose level. This patient developed a liver abscess that necessitated surgical drainage and intravenous antibiotics. Although these adverse events were possibly worse after SBRT/NFV, this was not considered directly caused by SBRT/NFV, given that all started prior to receiving SBRT/NFV. Of note, there were no statistical differences in any toxicities or grade ≥ 3 events based on NFV dosing or in patients receiving 5–6 Gy/fraction as compared to 7–8 Gy/fraction ($p > 0.05$ for both). Thus, the highest dose level (40 Gy in 5 fractions) tested in this investigation was considered the MTD (Supplementary Table 2).

The median follow-up was 14.4 months (range, 1.0–45.7); all patients had passed away at the time of data analysis. Fig. 2 illustrates outcomes following SBRT/NFV. Six (15%) patients experienced any local failure. The median DFFS was 11 (95% confidence interval (CI), 7–15) months, and most distant metastases occurred in the liver, peritoneum, and/or lung. The median FFS was 10 (95% CI, 6–14) months. The median OS in all patients was 14 (95% CI, 12–18) months. Most patients died from disease, but five patients died from late gastrointestinal (GI) bleeding ($n = 2$ superior mesenteric artery pseudo-aneurysm (bleeding was stopped after SMA stent placement in both cases, but both families chose to pursue comfort care measures), $n = 1$ unknown location (patient refused esophagogastroduodenoscopy (EGD)), $n = 1$ lower GI location with negative EGD, $n = 1$ disease progression invading the GI tract on EGD). Thus, aside from the patient with clear EGD evidence of bleeding from disease progression, the remainder four may have possibly experienced late grade 5 events. However, although treatment effect can never be entirely excluded, it was the consensus of the multidisciplinary management team that one of these patients had a lower GI bleed with negative EGD, which could be from lower dose spillage to other portions of the bowel, but would not be as likely as areas exposed to higher dose. Another patient had bleeding of an unknown location, but had undergone pancreaticoduodenectomy (and thus removal of the area exposed to high dose).

To further explore patients that developed GI bleeding, a dosimetric analysis was performed between four patients that experienced bleeding (having excluded one patient whose bleeding was unequivocally visualized secondary to disease progression) and 23 patients without bleeding who received 35–40 Gy (Table 3). Although no values were statistically significant, there were trends toward significance in multiple parameters, most notably duodenal V35, V20, and V10.

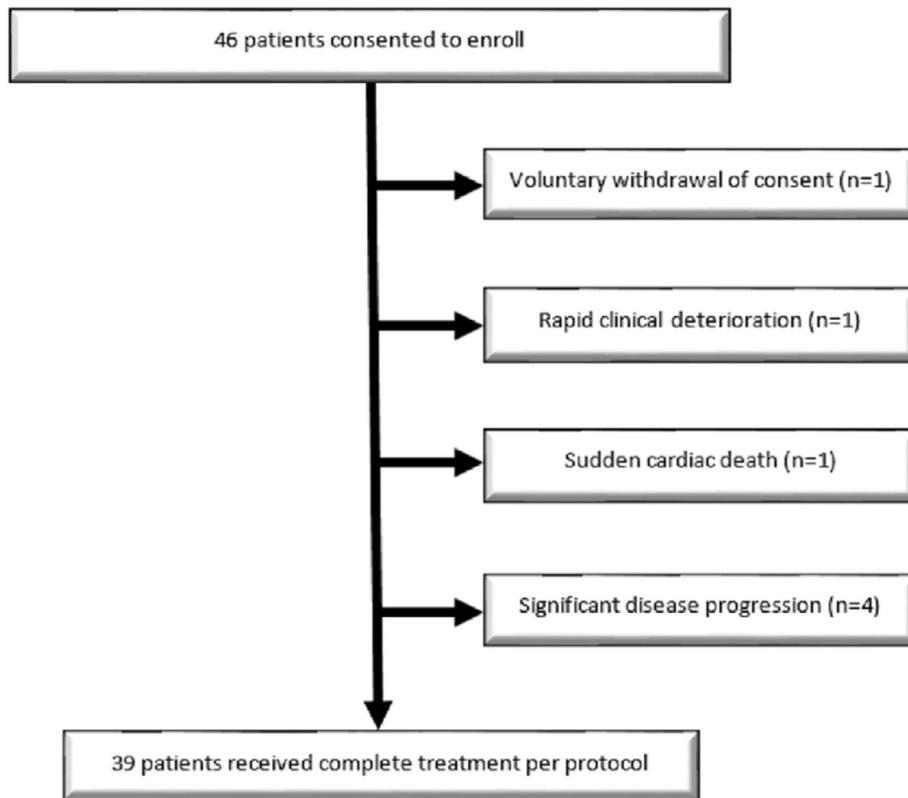


Fig. 1. Study schema.

After completing SBRT/NFV, 10 patients were found to have metastases (4 by imaging, 6 by exploratory surgery), 15 were deemed to have unresectable disease (6 by imaging, 9 had attempted pancreaticoduodenectomy), and 1 had declining performance status. Thirteen patients were thus considered resectable after therapy; 1 refused surgery and therefore twelve underwent pancreaticoduodenectomy (eleven with negative margins and six with positive nodes). Of these 12 patients, 9 were initially borderline resectable and 4 unresectable; all but one received 7–8 Gy per fraction. There was no 30-day postoperative mortality.

Of the 12 resected patients, 1 had no response, 6 had Evans grade IIa response (10–50%), 4 had Evans grade IIb (50–90%) response, and 1 had a complete response (Supplementary Table 3). Linear regression analysis of the pathological response score and combined SBRT/NFV dose revealed a positive correlation with a slope of 0.24 (Supplementary Fig. 1).

Fig. 3 shows the Kaplan–Meier OS curves of patients that received surgery versus lack thereof (Fig. 3A), along with a comparison of the 5–6 Gy and 7–8 Gy cohorts for patients with unresectable disease (Fig. 3B). The median OS for those undergoing surgery was 19 (95% CI, 12–30) months, which was statistically similar to unresected patients (median OS 14 months, 95% CI 8–24 months) ($p = 0.11$). In the unresected cohort, as compared to those receiving 5–6 Gy (median OS 10 months, 95% CI 4–13 months), there was higher OS in whom 7–8 Gy (median OS 18 months, 95% CI 12–24 months) was delivered ($p = 0.002$). Local failures in these cohorts could not be reliably compared owing to the relatively few events.

Discussion

Novel radiosensitizers such as NFV may be advantageous when combined with ablative RT for LAPC, but there are no such reports

to date. The results of this phase I trial demonstrate that this approach is well tolerated, including at the maximum dose level (40 Gy in 5 fractions combined with 5 weeks of 1250 mg twice daily NFV). However, late gastrointestinal bleeding was found to occur herein, which must be further addressed. Therefore, further prospective investigations utilizing SBRT/NFV are recommended to follow-up these results.

Evaluating the safety and efficacy of SBRT regimens utilizing 7–8 Gy/fraction is important, especially in the presence of a candidate radiosensitizer. This is primarily because 5–6 Gy/fraction dosing yields biologically effective doses (BEDs) that are similar to palliative (<45–50 Gy) conventionally fractionated regimens, with similar results [36]. Although this study was not powered to compare outcomes, it is hence not surprising that there was a trend toward improved OS in unresected patients receiving 7–8 Gy/fraction over 5–6 Gy/fraction. Although OS (which can be influenced by a multitude of factors) is acknowledged as a suboptimal endpoint for this comparison as opposed to local recurrence, it was notable that relatively few patients had local recurrences herein; whether the presence of NFV was a causative factor cannot be addressed by this nonrandomized study. Nevertheless, the local control herein compares favorably to an existing phase II trial showing 1-year freedom from local progression of 78% (2-year value of 83% in this study) [37]. Although that trial used 33 Gy in 5 fractions, there are other currently ongoing trials seeking to escalate doses up to 60 Gy in 5 fractions [38].

Another option that may prove advantageous to improving the therapeutic ratio is simultaneous integrated boosting (SIB), especially because there is evidence for improved outcomes with dose-escalated therapy (albeit in the conventionally fractionated setting) [39]. A “threshold” of ~100 Gy has been posited to achieve optimal and durable tumor control, but has not been well-validated for pancreatic cancer [36]. Because this threshold

Table 1
Selected clinical characteristics of the study population.

Parameter	Count (Percent)
Age (years)	
Median (range)	63 (35–80)
Gender	
Male	23 (59%)
Female	16 (41%)
Race	
Caucasian	37 (95%)
Other	2 (5%)
ECOG performance status	
0	13 (33%)
1	21 (54%)
2	5 (13%)
Tumor size (cm)	
Median (range)	3.1 (0.6–6.5)
Initial resectability status	
Borderline resectable	22 (56%)
1) Contact with SMV/PV > 180°	6
2) Contact with SMV/PV ≤ 180° with irregularity or thrombosis of vein(s)	4
3) Contact with IVC	1
4) Contact with SMA or CA ≤ 180°	4
5) Contact with CHA/variant arterial anatomy	7
Unresectable	
1) Contact with SMA > 180°	17 (44%)
2) Contact with CA > 180°	116
Clinical T classification	
T3 (extending beyond pancreas but not involving SMA/CA)	18 (54%)
T4 (involving SMA or CA)	21 (46%)
Clinical N classification	
N0	22 (56%)
N1	17 (44%)
PTV size (mm ³)	
Median (range)	125 (37–278)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SMV, superior mesenteric vein; PV, portal vein; IVC, inferior vena cava; SMA, superior mesenteric artery; CA, celiac artery; CHA, common hepatic artery; PTV, planning target volume.

Table 2
Instances of toxicities possibly, probably, or definitely attributed to protocol therapy during and 30 days post stereotactic radiotherapy.

Adverse Event	Grade 2	Grade 3	Grade 4
Abdominal pain		1	
Alkaline phosphatase elevation		1	
Anemia	3*	1	
Anorexia	2*		
Constipation	1		
Dehydration	3		
Deep vein thrombosis-femoral		1*	
Emesis		1	
Fatigue	2	1*	1
Fever	1		
Hyperbilirubinemia	1		
Hypoalbuminemia	2**		
Hypokalemia		1	
Hypotension	2		
Infection	1		1
Leukopenia	2	1	
Nausea	1		
Sepsis		1	
Thrombocytopenia		2	
Total	21	11	2

*Denotes one patient who experienced this adverse event after 30 days following SBRT completion.

corresponds to a 5-fraction total dose of 50 Gy, the potential utility of a radiosensitizer to possibly decrease this “required threshold” would be noteworthy if eventually proven.

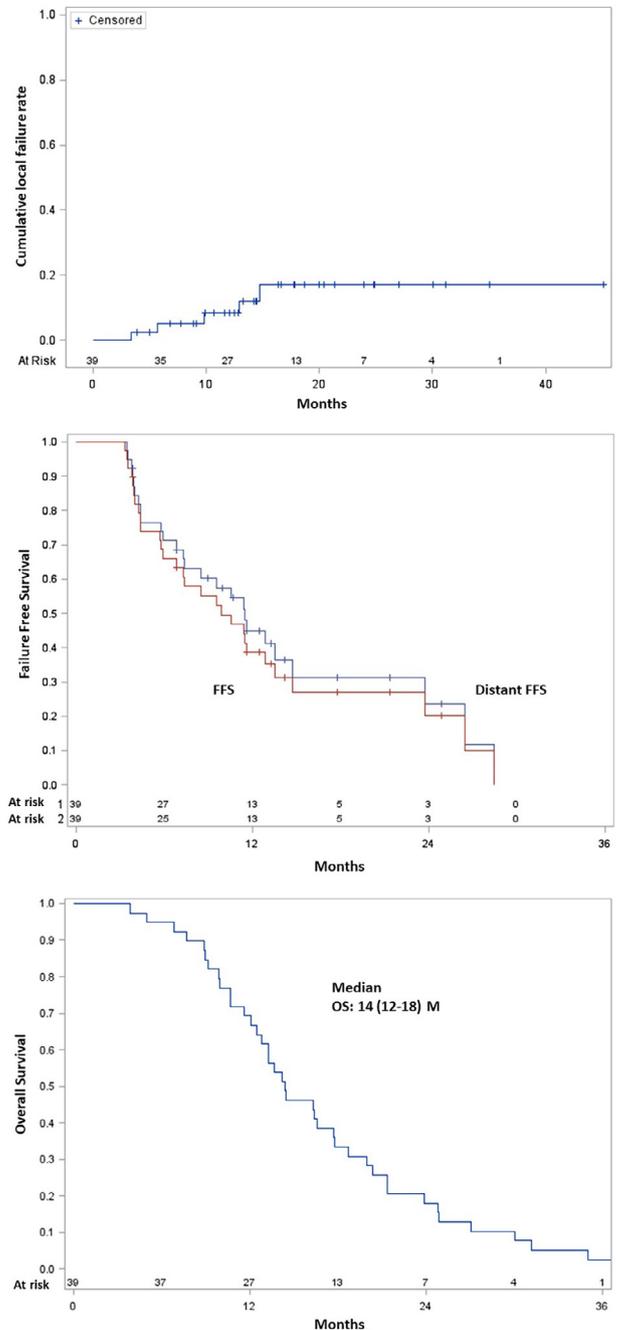


Fig. 2. Cumulative incidence curve of local failures (A), Kaplan–Meier’s survival curves of distant failure-free survival and (overall) failure-free survival (B), and Kaplan–Meier’s overall survival curve (C).

The proportion of initially BR and UR patients able to undergo resection, along with R0 resection rates, in this trial was also comparable or numerically higher than those of many prospective trials [1]. To this extent, it is noteworthy that all but two patients able to undergo pancreaticoduodenectomy received 7–8 Gy/fraction. Although this may indicate that dose-escalated SBRT can better address vascular-abutting disease, meaningful statistical comparisons (e.g. local recurrence) cannot be performed owing to the low sample sizes. SBRT dose-escalation to vascular areas can also be performed by means of SIB to the tumor-vessel interface, which is a frequent area of positive margins at time of resection [40].

Our outcomes with 7–8 Gy/fraction SBRT and NFV (median OS 18 months) are numerically higher than existing data [37] and

Table 3
Dosimetric analysis of patients receiving 7–8 Gray per fraction with gastrointestinal bleeding versus lack thereof.

Parameter median (range)	Patients without GI bleeding (n = 23)	Patients with GI bleeding (n = 4)	p-Value (Mann-Whitney U)
PTV (cc)	122 (119–157)	138 (37–218)	0.891
PTV mean dose (Gy)	41 (38–41)	42 (36–45)	0.260
Duodenum (cc)	72 (66–88)	75 (66–91)	0.585
Duodenal mean dose (Gy)	19 (18–21)	22 (19–26)	0.116
Duodenal V35 (cc)	7 (7–11)	15 (7–21)	0.056
Duodenal V30 (cc)	18 (16–21)	25 (17–32)	0.101
Duodenal V25 (cc)	27 (25–32)	39 (25–51)	0.117
Duodenal V20 (cc)	39 (35–44)	51 (34–66)	0.088
Duodenal V15 (cc)	48 (43–53)	57 (43–71)	0.128
Duodenal V10 (cc)	51 (46–58)	61 (52–72)	0.076
Duodenal V5 (cc)	55 (50–62)	65 (57–74)	0.101

Abbreviations: GI, gastrointestinal; PTV, planning target volume; cc, cubic centimeters; Gy, Gray; V_n , volume of organ receiving at least n Gy.

similar to those of the prospective ARCI study for LAPC (17 months) [23], which consisted of concurrent NFV and conventionally fractionated (50.4 Gy, boosted to 59.4 Gy). Although our FFS of 10 months was nearly double the progression-free survival of 5.5 months in that study, there are many confounding factors that preclude direct comparison, including definition and measurement of recurrent/progressive disease. However, our acute toxicity outcomes roughly appear comparable or even numerically favorable to those data. Although this could be related to utilizing a stereotactic technique, that study performed some degree of elective nodal irradiation without further nuances of treatment planning reported.

The finding of five patients dying from late gastrointestinal (GI) bleeding must be qualified. We first acknowledge that the occurrence of superior mesenteric artery pseudo-aneurysms ($n = 2$) is a characteristic of radiation-induced vascular injury, as seen in several other neoplasms [41–51]. Indeed, using these examples, carefully measuring doses to arterial structures may be of benefit, especially in the setting of high doses per fraction. Whether normal tissue complications depend on the caliber of the particular blood vessel remains an ongoing issue, however. Nevertheless, assuming that the patient with EGD evidence of bleeding from progressive disease as well as the subject with EGD-negative lower GI bleed were highly unlikely related to SBRT/NFV, the rate of 8% (3/39 patients) herein may be higher than the work of Herman and colleagues [37] (4%, 2/47 patients). Although NFV cannot be ruled out as an associated factor, it is important to contextualize that the cone-beam computed tomographic image guidance in that study was likely superior to the orthogonal kilovoltage imaging herein. Additionally, that trial prescribed 33 Gy over 5 fractions, whereas most (72%) patients in this trial received 35–40 Gy over 5 fractions; of the five patients that experienced bleeding herein, four received 40 Gy and the other 35 Gy. Despite the lower sample sizes, there were trends toward statistical significance of multiple dosimetric parameters and bleeding. Hence, we endorse careful consideration of stricter constraints as well as measuring other parameters such as doses to the superior mesenteric vessels. Our current recommendation for the GI tract constraint is that no more than 0.5 cc of the stomach/small bowel receives higher than 32 Gy. With this constraint, we have treated over 20 patients with 40 Gy in 5 fractions in institutional phase II trials without further late GI bleeding.

There are multiple possible sources reducing applicability of these data in addition to those mentioned above. The prophylactic use of a proton inhibitor and selection of patients without significant bowel/ulcerative disease should be noted, along with the individualized judgment regarding PTV margins and target coverage versus bowel doses. Next, as other work has pointed out, there is an inherent difficulty in evaluating acute versus late toxicities owing to the nature of follow-up as well as death [37,52], which is why adverse events were reported as an aggregate, similar to other investigations [23]. Additionally, subgroup evaluation of survival by dose per fraction is largely a post-hoc analysis with nonrobust sample sizes. Lastly, the individual effect of NFV on any assessed endpoint cannot be ascertained owing to the non-randomized nature of this prospective trial.

Disclaimers

A portion of this work was presented at the 2011 & 2018 Annual Meeting of the American Society for Radiation Oncology and 2014 Gastrointestinal Cancers Symposium sponsored by the American

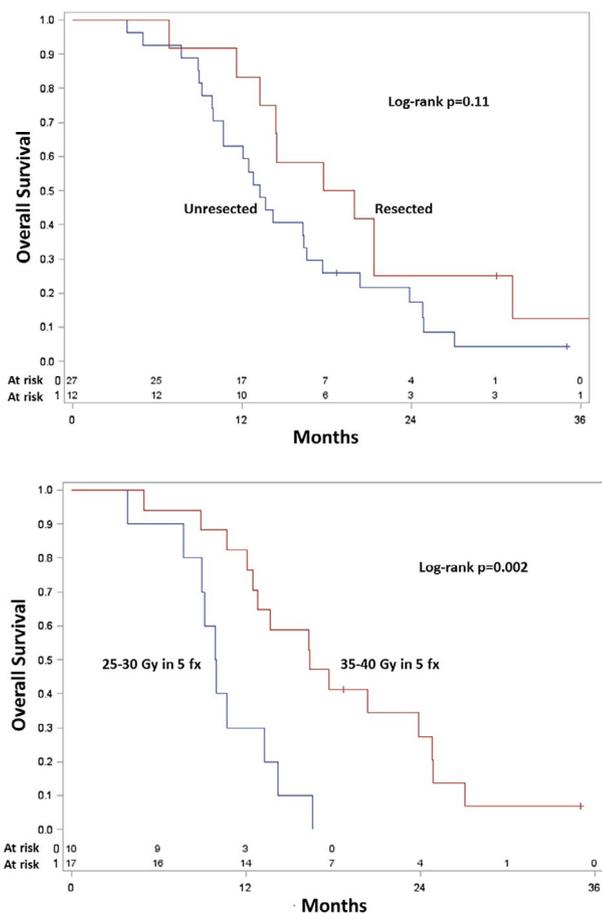


Fig. 3. Kaplan–Meier's overall survival curves of patients having undergone surgical resection versus lack thereof (A), and unresected patients having received 7–8 Gy/fraction versus 5–6 Gy/fraction.

Society of Clinical Oncology, the American Society for Radiation Oncology and the Society of Surgical Oncology.

Conflicts of interest

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2018.11.002>.

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